DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

Monday, September 9, 2002

10:30 a.m.

Hilton Washington DC North
629 Perry Parkway
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

Warren K. Laskey, M.D., Acting Chairperson

Elisa Harvey, DVM, Interim Executive Secretary
Geretta Wood, Executive Secretary

VOTING MEMBERS:

Salim Aziz, M.D.
Julie A. Freischlag, M.D.

CONSULTANTS:

Bruce A. Perler, M.D.
Anthony Comerota, M.D.
Christopher J. White, M.D.
Kenneth E. Najarian, M.D.
Anne C. Roberts, M.D.
Michael J. Pentecost, M.D.
Kent R. Bailey, Ph.D.
Anton Sidawy, M.D.
Ileana Pina, M.D.

CONSUMER REPRESENTATIVE:

Robert A. Dacey

INDUSTRY REPRESENTATIVE:

Andrew K. Balo

FOOD AND DRUG ADMINISTRATION:

Bram Zuckerman, M.D.
Doyle Gantt
Dorothy Abel
Paul Chandeysson, M.D.

C O N T E N T S

P R O C E E D I N G S

DR. LASKEY: It is time for us to come to order. The topic to be discussed today is the premarket application for the Gore bifurcated endoprosthesis, P020040. I would like to have the executive secretary read the conflict of interest statement now.

DR. HARVEY: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. The agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Therefore, a waiver has been granted for Dr. Bruce Perler for his interest in a firm that

could potentially be affected by the panel's recommendations. The waiver involves a grant to his employer for a competitor study in which he is not involved in data generation or analysis, and for which funding is less than $100,000 per year. Copies of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Julie Freischlag, Kenneth Najarian, Anne Roberts and Michael Pentecost. Each of these panelists reported interest in firms at issue but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

The agency also would like to note that due to the regulations governing covered relationships, the panel chair, Dr. Cynthia Tracey will not participate in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion

will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. LASKEY: Thank you. I would like to have the panel members now introduce themselves, beginning to my right, please.

MR. BALO: Andy Balo, DexCom, Inc., industry rep.

DR. AZIZ: Salim Aziz, clinical associate professor, University of Colorado.

DR. COMEROTA: Anthony Comerota, vascular surgeon, director of the Jobst Vascular Center and professor at University of Michigan, Ann Arbor.

DR. PENTECOST: Michael Pentecost, professor and chairman of radiology at Georgetown.

DR. BAILEY: Kent Bailey, biostatistician, Mayo Clinic.

MS. WOOD: Geretta Wood, executive secretary.

DR. HARVEY: Elisa Harvey, interim executive secretary for this panel meeting.

DR. LASKEY: Warren Laskey. I am an

interventional cardiologist from Baltimore.

DR. SIDAWY: Tony Sidawy. I am chief of surgery at the VA Medical Center here, and professor of surgery at George Washington and Georgetown Universities.

DR. FREISCHLAG: Julie Freischlag. I am a vascular surgeon and chief of vascular surgery at UCLA.

DR. NAJARIAN: Kenneth Najarian, interventional radiologist and professor of radiology at the University of Vermont.

DR. ROBERTS: Anne Roberts, interventional radiologist and professor and chief of vascular and interventional radiology at UC San Diego.

DR. PERLER: Bruce Perler, chief of vascular surgery at Johns Hopkins.

DR. WHITE: I am Chris White. I am an interventional cardiologist, and I am from the Ochsner Clinic in New Orleans.

MR. DACEY: Robert Dacey, consumer representative, Boulder County, Colorado.

DR. ZUCKERMAN: Bram Zuckerman, director, Division of Cardiovascular Devices, Food and Drug Administration.

DR. LASKEY: Thank you, all. Elisa, would

you read the voting status please?

DR. HARVEY: Yes. This is an appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for this meeting, on September 9th, 2002: Anthony Comerota, Christopher White, Kenneth Najarian, Anne Roberts, Michael Pentecost, Bruce Perler, Kent Bailey and Anton Sidawy.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. In addition, I appoint Dr. Warren Laskey to serve as panel chair for the duration of this meeting.

It is signed by Dr. David Feigal, Director for the Center of Devices and Radiological Health, August 30th, 2002.

In addition, I have another voting status to read: Pursuant to the authority granted under

the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 22, 1990 and as amended August 18th, 1999, I appoint the following individual as a voting member of the Circulatory System Devices Panel for the meeting on September 9th, 2002, Ileana Pina, M.D.

For the record, Dr. Pina is a consultant to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research. She is a special government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. It is signed by William Hubbard, Senior Associate Commissioner for Policy and Planning, on behalf or Linda Skladany, Senior Associate Commissioner for External Relations, September 2, 2002.

DR. LASKEY: Thank you. At this point I would like to open this portion of the meeting, the public hearing, and to ask the audience if there is anyone who wishes to address the panel on the day's topic preferably. Dr. Rodney White had sent a letter requesting time before the panel. Is Dr. White in the audience?

Open Public Hearing

DR. RODNEY WHITE: Yes. My name is Rodney White. I am a vascular surgeon from Harbor UCLA. I am a member and chairman of the Lifeline Registry Committee, which is the topic for today; secretary of the Society for Vascular Surgery. I think my greatest conflict is that I am a clinical vascular surgeon who makes my living implanting these devices and showing up at meetings like this, and I have been the PI or co-investigator in many of the clinical trials that are currently under evaluation.

[Slide]

What I wanted to speak to you briefly about this morning is the Lifeline Registry. This is a project that was initiated back in 1998, prior to the approval of any of the endoluminal graft devices. At that particular time there was interest by not only the manufacturers and the clinical investigators but by the various agencies, and particularly the FDA, to look at issues that may be developed and related to endoluminal vascular grafts.

[Slide]

The Lifeline Registry goals were to do two

things, to provide a longitudinal observational database where endoluminal graft performance could be defined and evaluated and then, secondarily, over time, as will become apparent during today's talk, that there are surveillance issues that need to be addressed to follow these patients appropriately, and the attempt, again, from this multifacet aspect was to develop those as issues arise and make clinical tools that could easily follow these patients available.

[Slide]

The Lifeline Registry has other aspects to it. The web page which is, again, supported by the industrial partners and by the SVS and AVS, has not only patient information but updates data on a six monthly basis from the Registry. This is published not only in the Journal of Vascular Surgery but is also updated periodically so that the data is available to everybody.

[Slide]

As I have mentioned before, the mission is to provide longitudinal consecutive data, and with reference to the panel meetings all of the manufacturers that have received approval and the data set that will be presented today will become

part of the Registry. There is an option for the manufacturers to be able to use the Registry for storage of their postmarket surveillance data, and that makes then an easily available, and because of the high level of compliance that goes with these studies, reliable database to make these long-term observations.

There are also initiatives to work with the new VA cooperative study which was recently approved, and with our Canadian collaborators who have similar studies, so that the attempt would be on a voluntary basis to have a very large registry of data at a high compliance level to address issues as they develop.

[Slide]

The key stakeholders then are the clinicians in the societies, the Lifeline Foundation which is the funding arm of the SVS that our industrial advisory committee is made up of. All of the major manufacturers are participating in this, and the federal agencies, including NIH, FDA and CMS, have ex officio seats so that, hopefully, all of the relevant individual people are there.

[Slide]

With regard to surveillance, this is a big

clinical problem. We are relying on CT imaging. There is a major amount of data that is required, and the issues involved are at many levels, all the way from patient compliance to storage and efficient cost and effective relay of this to a site that could be accepted.

[Slide]

I list here the major manufacturers who have throughout this project supported this. Again, this effort was initiated in 1998 prior to any endoluminal graft being implanted. So, one of my comments would be that from all respects this is an effort by industry and by the agencies to be very proactive in terms of following these patients.

[Slide]

I show you an example of a patient who has had a device for six years. The issues related to imaging and what happens to that aneurysm over time are particularly relevant, and it is a new scenario we have not dealt with before. There are many measurements involved in this; what happens to the aneurysm and the fixation sites? Are there leaks? Are the grafts patent? Things that we have never dealt with before clinically.

[Slide]

Through an interactive system that is developed to be able to collect this data from initial paper forms and now through an electronic format, the attempt is to make available not only to the manufacturers and the agencies through the PMA data sets that are stored in the Registry, but also as a clinical tool that could be developed for surveillance mechanisms.

[Slide]

I had mentioned to you that in the Journal of Vascular Surgery there is a publication every six months. This is just one of the tables from the March issue of this last year, which shows that there are 1600 patients now. We are also looking at control patients that become available and as the data set grows, this now is the highest compliance and the largest volume of patients that is available with follow-ups in the three- to-six year range. So, this is becoming quite mature and able to address many of the issues.

[Slide]

All the data is stored on a web site through the New England Research Institute, which is our administrative arm.

[Slide]

It has a secured site that enables us to do that, and through a series of tables, and I won't go through it, there is data on each patient relevant to measurements.

[Slide]

And then corresponding imaging is stored so that it is readily available, able to be analyzed in retrospect.

[Slide]

To summarize this, what I would say is that there are two papers I would refer you to, one in the Journal of Vascular Surgery, one that globally describes the Registry and how it operates, and the second one, which is the first data report that was published in June--this will be the format again, every six months all the data published on the web site, accessible and for relevant questions from anyone that could be addressed. These are unauthored publications in an attempt to make this readily available.

[Slide]

If anyone is interested in contacting the New England Research Institute, which is the administrative arm, they can supply more

information. Thank you for the opportunity to present this.

DR. LASKEY: Thank you. Are there any questions from the panel members?

DR. COMEROTA: Rod, that is a nice review. You mentioned that patients who were so treated with endografts would become part of the Registry, but then you also went on to say that it is voluntary. Could you just clarify that please?

DR. RODNEY WHITE: Yes, there are actually two parts to the Registry. The first part, which we call Part A, is similar to what you are going to hear today, the data set that is submitted for the PMA submissions. For Medtronic and Guidant, following their approval in 1999, they have continued to update their data. So, that is the Registry data set. After today, will be the submission of the Gore data and with subsequent instances we will, hopefully, be able to get all the manufacturers' data so that there is voluntary compliance of their submissions, although they can--and if the way I say this isn't correct, please, the agency will tell me, but they have offered to the manufacturers that they can use the Registry to store their data. When they store the

data they can download it by the automated system and use that as part of their annual reports. In that way, it is then made a very high compliance level data set across the industry, available to everybody to view the data, to be able to see how that works.

So, it is voluntary and each manufacturer can do this on their own but, again, I would emphasize there has been an effort across the industry to do this in collaboration before it even became an issue.

Secondarily, the clinical tool that is available is available to individual practitioners and that, obviously, would be voluntary but we offer that. We ask them to consent their patients according to the IRB regulations so that we can follow those folks over time. There is also even a new ability that has been worked out for investigator IDEs to capture that data by the same mechanism. So, it is voluntary but has turned out to be a good repository and, hopefully, a way to work issues through all the relevant parties to solve any problems that come up.

DR. LASKEY: Thank you. This is a very important area. Dr. Zuckerman?

DR. ZUCKERMAN: Yes, Dr. White has indicated one possible mechanism or pathway by which manufacturers, after device approval, have periodically updated the agency with required data. This isn't to say, however, that this is the only way it can be done. From the agency's perspective, with the other two mentioned manufacturers we were interested in periodic update reports. What you have heard here is one mechanism for generating such data.

DR. LASKEY: I just have one final question, if I might. Maybe I missed it on the slide, but the support for this Registry derives from?

DR. RODNEY WHITE: There are two sources of funding. The first is an ongoing commitment from the Society for Vascular Surgery and American Society for Vascular Surgery, which is from the Lifeline Foundation itself, the funding arm. The major funding comes from what we call the industrial advisory committee, which is constituted of each of the major manufacturers that make these devices. They all, to a company, have on an annual basis now, for four years, supported that effort. So, the finances are between the academic

societies, the Lifeline, and the manufacturers.

DR. LASKEY: Thank you very much.

DR. RODNEY WHITE: Thank you.

DR. LASKEY: Are there any other members of the audience requesting time?

[No response]

Again, thank you, Dr. White. I would like to close this portion of the open public hearing and move on. I would like to move to the sponsor's presentation at this point. I just want to remind people, we are shooting for a twelve o'clock break for lunch, to stay on schedule. Dr. Harvey?

DR. HARVEY: Please remember to introduce yourself when you come to the podium to speak, and to state your conflict of interest and also to use the mike whenever you are asked any questions and need to come forward.

Sponsor Presentation

Introduction

MR. SININGER: Good morning.

[Slide]

I am John Sininger, with W.L. Gore & Associates. I am responsible for Gore's Medical Products Division. W.L. Gore is the sponsor for this premarket application for the Excluder

Bifurcated Endoprosthesis. Because this is such a mouthful, we will be referring to this frequently in the presentation as EBE. So, as you hear that through the presentation you will know what we are referring to.

[Slide]

Gore is a 44-year old high technology company engaged in the development, manufacturing and sales of a broad range of high technology products. Gore's history and our reputation in all the markets that we serve is that we provide only the highest quality and highest performance products in all of the markets that we serve. Gore provides a broad range of products, from sophisticated aerospace applications to Gortex fabrics, which most people know Gore by, to microfiltration, industrial filtration products and, of course, Gore's Medical Products Division which is presenting this presentation today.

[Slide]

Gore Medical has been in the business of developing, making and selling products for almost 25 years, over 25 years. In that period of time Gore has developed many products that really serve many different patient populations, and Gore was

actually a real pioneer in some of the early work for products to repair peripheral vasculature.

[Slide]

In this period of time there have been over seven and a half million clinical implants of Gore medical products worldwide. The significance of this is that this clinical background offers us a clear understanding of the need for a safe and effective treatment for abdominal aortic aneurysm repair.

I have had the privilege of being with Gore and Gore's Medical Products Division for 25 of those years. I recall being part of some of the very early development work for not only our peripheral vascular grafts but also our first aortic graft. It was a real pleasure and a privilege to be able to provide a product that made such a significant difference to patients with this life-threatening AAA disease. It is even more significant for me today, 25 years later, to be standing here, introducing our presenters with a product that we believe makes an even greater difference to the patients who receive these products. We have seen these products make a real difference in the lives of patients who are

receiving these devices.

It is for this reason that I am very excited about the opportunity to be here to introduce our presenters who will be presenting data which we believe supports the primary safety and efficacy of the device. We hope your review of the data substantiates that conclusion.

[Slide]

Our agenda today is that Dave Williams, who is a Gore associate, will be presenting an overview of the device and study overview. Dr. David Brewster, from Harvard Medical School, will be providing a background to abdominal aortic aneurysm repair. Dr. David Naftel will be talking about trial design and trial management. Finally, Dr. Jon Matsumura, who is also our principal investigator, will be presenting the clinical results.

In addition to these individuals, there are a number of clinical investigators who are here, as well as a number of other Gore associates who are here to answer any questions you may have.

Finally, I would like to sincerely thank all of you, the FDA, for all your time and consideration and efforts in reviewing all this

data, and look forward to a lively discussion and your conclusions. Thank you. Dave Williams?

Product and Study Overview

MR. WILLIAMS: Thank you, John.

[Slide]

Good morning and thank you, ladies and gentlemen of the panel for the opportunity to present today.

[Slide]

I will do a quick overview of the Excluder Bifurcated Endoprosthesis, or EBE, device description including its deployment; briefly summarize the preclinical evaluation; and then provide a brief overview of the clinical evaluation experience.

[Slide]

The device design is bifurcated, modular and it has a fully supported self-expanding nitinol stent which basically supports an EPTFE or PTFE vascular graft on the blood contact surface.

These are the various components of the modular device. You can see the two primary components. We have the trunk ipsolateral leg. We have the contralateral leg. We have an aortic extender and an iliac extender.

There is a unique feature in this device in that the outer nitinol stent is attached to the underlying PTFE graft material in a sutureless fashion. It uses fluoropolymer films to bond the stent to the underlying graft. At the proximal end or the aortic trunk end of the device you can see that there are anchors for active fixation, and there is also an external sealing cuff to aid in hemostasis relative to the proximal application of the device.

The device also relies on oversizing as part of the fundamental design performance in that you choose device sizes based on the patient's healthy anatomy in both the proximal aortic neck, infrarenal neck, as well as the common or external iliac vessels. So, the device is relying on both active and passive fixation and oversizing to create fixation and hemostatic seal to exclude the aneurysm.

[Slide]

This is a picture of the device's two main components as they would be assembled in situ. So, you have the trunk ipsolateral leg component with the contralateral leg component overlapping or docking into that primary component.

[Slide]

The device is loaded or constrained down onto a delivery catheter. The trunk ipsolateral leg component is constrained or loaded onto an 18 French delivery profile catheter. You can see here that there is a PTFE sleeve or corset that is used to hold the device on the catheter in the constrained position. That corset or constraining sleeve is laced in place with a single PTFE fiber which we refer to as the deployment line. That line runs the length of the delivery catheter and exits here, in the hub end or the operator end of the catheter, and is connected to this deployment knob. In the hub you can also see the Y valve or the Touhy-Bourst which contains the guidewire lumen, a fleshing port in addition to the deployment knob.

[Slide]

This is an image of the contralateral leg component partially deployed. This gives you a feel for the constraining sleeve as it is being unlaced through the deployment line retraction, allowing the nitinol stent to self-expand, deploying the device into position.

[Slide]

Next we will see a computer animation briefly of the positioning and deployment of the device in the infrarenal aortic anatomy. The anatomy is accessed by retrograde guidewire cannulation. Over the guidewire an 18 French vascular access sheath is placed into the infrarenal aortic anatomy. With the sheath in place, the trunk ipsolateral component can then be tracked into a proximate position. The vascular introducer sheath is withdrawn to expose the device. Then, under fluoroscopic visualization the proximal end markers and the contralateral and ipsolateral orientation markers can be located to properly position the direction of the deployment of the two limb components.

Once the device has been fine-tuned or positioned relative to the lowest renal artery and to proper lateral orientation of the limbs, the deployment knob is pulled; the corset opens and allows the self-expanding stent to actuate the device deployment.

Trunk ballooning is recommended at this point to further optimize the dilatation of the device. Contralateral access is gained via guidewire and central lumen position is confirmed.

Then, a 12 French sheath is placed inside the contralateral leg hole. The contralateral leg is delivered and deployed in similar fashion. Adjunctive ballooning in the top and bottom of the device is recommended, and adjunctive aortic extenders or iliac extenders may be placed to further optimize the procedure.

[Slide]

The preclinical evaluation summary is that all evaluations, including toxicology, biocompatibility, in vitro and in vivo tests demonstrate that the EBE system meets the functional requirements for aortic endovascular devices.

[Slide]

A quick overview of the various EBE clinical studies is listed here. The device that you are considering today is our first generation Excluder device which went through both European and U.S. feasibility trials starting in late '97 and ending in mid-'98.

The trial data under consideration today is the pivotal trial which effectively started to enroll patients in December of '98 and stopped enrolling patients in January of 2000. There was a

continued access portion to this pivotal trial and, subsequent to that, we have continued to study, in an IDE format, in the United States a second generation EBE device and those studies are ongoing.

[Slide]

The worldwide clinical experience with the EBE was initiated in Europe in September of 1997. The EBE has been commercially available outside the United States since 1998, and with the continuing U.S. clinical trial evaluations, combined with the rest of the world commercial use experience, we now have exceeded 4400 implants or in excess of 10,000 individual component pieces.

[Slide]

Refocusing back onto the pivotal study under consideration today, the data includes events through February 29th of this year. Although the primary and secondary hypotheses for the study were evaluated to a 12-month endpoint, the protocol amendments and patient consents allowed for patient follow-up out to five years of this particular patient cohort. Thank you for your attention.

Abdominal Aortic Aneurysm Background

DR. BREWSTER: Mr. Chairman, distinguished

panel members, good morning.

[Slide]

My name is David Brewster. I am a clinical professor of surgery at Harvard Medical School and at the Massachusetts General Hospital, in Boston where I also serve as director of endovascular surgery.

W.L. Gore has paid my expenses to be here with you today, but I have no financial interests in the device or the company, nor in the outcome of this meeting today.

I am a board-certified vascular surgeon with over 25 years of experience in the management of patients with abdominal aortic aneurysms. During this time, I have repaired approximately 1500 aneurysms by conventional open surgical graft repair, and during the last eight years I have had considerable experience with the alternative mode of therapy being considered today. During this time I have treated nearly 500 patients with endovascular grafts, employing a wide variety of different devices and participating as principal investigator in five FDA clinical Phase II trials including, of course, the Gore EBE trial being presented this morning.

In the next few minutes I will review some facts regarding aortic aneurysm in the hope that this information will serve as a backdrop or yardstick, if you will, by which to evaluate the results of the EBE clinical trial and, therefore, aid you in your deliberations.

Apologies in advance to those panel members already familiar with this material, but my goal is to ensure that all panelists are acquainted with basic facts regarding epidemiology and natural history of aneurysms, as well as the anticipated outcome of traditional open surgical repair.

[Slide]

Aortic aneurysms, no doubt, represent an important public health problem. Approximately 200,000 new cases are diagnosed in the U.S. each year and 50,000 procedures approximately are performed per year for aneurysm repair. The principal goal of these procedures is to prevent aneurysm rupture, which is the 13th leading cause of death in the U.S. and 10th leading cause if one considers only men over the age of 65 which, of course, is the most common patient cohort.

[Slide]

It is well recognized that aneurysms are

being encountered more frequently in contemporary practice. This is due to both better diagnosis and recognition by a variety of imaging techniques, as well as an apparent true increase in prevalence. This latter phenomenon appears largely attributable to the well-documented aging of our population. The occurrence of an aneurysm, as well as the rupture risk, are known to increase sharply with age. As a consequence of such trends, several projections indicate a substantial increase in the number of patients with aneurysms who will require treatment in the next several decades, many of them likely elderly and with co-morbidities that make them at increased risk for standard open repair.

[Slide]

The expected natural history of an aneurysm is gradual expansion leading to eventual rupture unless this process is interrupted first by death of the host or from another cause. The goal of treatment, therefore, becomes treatment to prevent rupture in susceptible individuals. Decision-making currently lacks true scientific precision and, rather, represents a reasoned balancing of estimated risks of rupture versus repair, and an individualized approach to each

patient is emphasized based upon his or her own age, co-morbid conditions and, very importantly, treatment preferences. Considerable clinical judgment remains vitally important in such decision-making.

[Slide]

Although a number of factors contribute to rupture risk, it is widely accepted that aneurysm size, as measured by maximal diameter, is the most important determinant of rupture risk. While it is well established that truly small aneurysms have a low risk of rupture, this risk begins to sharply increase after the aneurysm reaches 4.5-5.0 cm in size.

While the fairly wide range of estimated rupture risk, indicated here from literature review, indicates the considerable differences reported in the literature from one series to another, a recent meta-analysis indicates an annual rupture risk of approximately 10 percent per year for aneurysms in the size range typical of those treated in the EBE clinical trial, as will be presented shortly.

[Slide]

Left untreated, aneurysms in the size

range relevant to most clinical decision-making can be expected to enlarge approximately 10 percent per year in maximal diameter. Hence, for aneurysms typical of the EBE trial, enlargement of approximately 0.5 cm or 5 mm per year would be anticipated.

[Slide]

During the past five decades standard open operative repair has been well established as a very effective and durable method of repair. Despite this, however, considerable room for improvement in the outcomes of therapy continue to exist. Although many individual referral-based reports from institutions of excellence suggest mortality rates of open repair well below five percent, many recent population-based series from large statewide or national databases reveal a real-world mortality more in the range of five to ten percent even in current practice.

In addition, all vascular surgeons recognize the substantial morbidity and complication rates of this extensive standard repair. A rate that is often substantially higher in elderly patients are those with associated co-morbidities. Patients who are often a typical

cohort are a sizeable percentage of those requiring treatment. Even in the best of circumstances, recovering from open repair takes many months and, indeed, several recent quality of life studies indicate that a significant number of older patients never quite regain their preoperative baseline functional status.

For all of these reasons, many high risk patients are often currently denied open surgical repair and left with the fear and concern that rupture may unpredictably occur at any time.

[Slide]

The goals of endovascular repair are to achieve a repair quite similar to that of open graft insertion, but to accomplish this in a manner which is less invasive by working within the vascular system and using small incisions and rather minimal anesthesia. The endovascular device is placed within the aneurysm sac, and with secure anchoring and fixation above and below the aneurysm in relatively normal and healthy arterial segments exclusion of the weakened portion of the aorta from arterial circulation and pressure is achieved, thus, eliminating the danger of rupture.

[Slide]

I would like to conclude with a brief review of a concept which is unique to endovascular aneurysm repair, that of endoleak. Endoleak denotes continued perfusion of the aneurysm sac as detected by one of several imaging modalities. Endoleaks have been classified by the source or cause of such failure to totally exclude the aneurysm from the circulation. Type IV leaks refer to those with transgraft seepage which may occur as an early phenomenon in devices constructed of porous fabrics. These are usually self-limited and of little to no clinical importance. In contrast, type I leaks are those due to failure to achieve a hemostatic seal at either the proximal or distal attachment zones, while type III leaks refer to leakage or continued perfusion of the sac caused by defects in the graft material itself or leakage at junction points of modular devices.

Because both of these types, type I and type III leaks transmit full arterial pressure to the aneurysm sac, both are generally accepted as potentially dangerous and an indication for further intervention.

In contrast, type II leaks are caused by reversed flow in normal arterial branches which may

remain patent. When the aneurysm is excluded by the endoluminal device and pressure falls to low levels within the sac normal antigrade flow may reverse and lead to continued perfusion via lumbar arteries or patent inferior mesenteric vessel.

Unlike type I and type III leaks, however, the clinical significance of the common type II endoleaks is much more uncertain as many seal spontaneously at later intervals and undesirable clinical outcomes, such as further growth and aneurysm rupture, are very infrequent.

[Slide]

In summary, pertinent facts to remember as we hear the results of the EBE clinical trial are that aneurysms of the 5-6 cm size range, typical of those aneurysms treated in the trial, enlarge on an average rate of approximately 10 percent or half a centimeter a year and carry an annual rupture risk of approximately 10 percent per year. Obviously, the therapy seeks to alter and improve on these natural history behaviors.

Although open surgical repair remains a very effective and durable treatment, morbidity and mortality risks remain substantial and other limitations exist. In appropriate patients

endovascular repair offers a safe and effective alternative with many potential advantages. Thank you.

Trial Design and Study Management

DR. NAFTEL: My name is David Naftel, and I appreciate this opportunity to speak to you.

[Slide]

I am a consultant for W.L. Gore and I have no financial interest except fee for service. I am a professor of biostatistics and professor of surgery at the University of Alabama in Birmingham. I will be discussing the trial design and study management this morning.

[Slide]

The first indication for use, the Excluder Bifurcated Endoprosthesis is intended to exclude the aneurysm from blood circulation in patients diagnosed with infrarenal AAA disease and who have appropriate anatomy. It is this indication for use that drives the corpus of this study.

[Slide]

So, the purpose of the study that we will discuss this morning is to determine the efficacy and the safety of the EBE for the primary treatment of infrarenal AAA.

[Slide]

There are two main hypotheses. The primary safety hypothesis is that subjects treated with the EBE have a proportion of major adverse events that is less than subjects treated with open surgical repair as evaluated through 12 months. A major adverse event is defined as any one of the following: First, requires therapy and short hospitalization; or requires major therapy and unplanned increase in level of care and prolonged hospitalization; or permanent adverse sequelae or death.

[Slide]

The primary efficacy hypothesis is that the EBE is an effective treatment method to exclude the aneurysm from blood circulation when used in the primary treatment of infrarenal AAA as evaluated at 12 months. Efficacy is defined as all of the following: Absence of endoleaks with or without treatment; absence of aneurysm enlargement, defined as greater than or equal to 5 mm; and absence of major device efficacy complications.

[Slide]

There are also secondary hypotheses. That is, compared with the control subjects, the EBE

subjects will have shorter stay in the intensive care unit; shorter hospital length of stay; and they will return to normal activities faster.

[Slide]

Here is the study design. It was a multicenter, prospective, intent-to-treat design. It is non-randomized but there are concurrent open surgical controls. The hypotheses are all focused on a 12-month duration. There is an independent core lab at Cleveland Clinic Foundation. There is a clinical events committee to review the major and minor adverse events, and then a data safety monitoring board to continually monitor the safety of the study.

[Slide]

The primary safety and efficacy endpoints that were focused on in designing the study were, first of all, a 15 percent difference in major adverse events between the two groups at one year and at least an 80 percent primary efficacy success also at one year. The 15 percent difference was used in the calculation of the sample size and it produced a minimum number of available subjects at one year to be 78 control patients and 156 EBE patients. This was based on a two-sided comparison

with an alpha level of 0.05 and 80 percent power. We used a ratio of two EBE to one control subject.

[Slide]

Standard statistical methods were used. Multivariable analyses were used to produce risk-adjusted comparisons of the two groups. These included both logistic regression and Cox proportional hazard. For the time-related events we used Kaplan-Meier for time to death and also time to first major adverse event. The Nelson method was used to produce cumulative adverse events across time on a per patient basis. Other standard methods were used to compare the two groups.

[Slide]

A number of inclusion and exclusion criteria were used, and here I will focus only on the anatomic criteria. For the control group only there had to be planned or expected use of infrarenal clamp. For the EBE group there had to be proximal aortic neck length greater than or equal to 15 mm; a proximal aortic neck angulation less than 60 degrees; and no significant thrombus at the arterial implant site.

[Slide]

Here are the follow-up requirements in the study that were adhered to. Contrast-enhanced CT was performed at one month in the EBE group; at three months if an endoleak had been found at one month; and then also a CT at six months and at one year and annually. The one-year and annual CTs were performed also for the control subjects.

Abdominal x-rays were performed at discharge in the EBE group and again at six months and annually. Bilateral ankle brachial index and physical exams were conducted in both groups at discharge, one month, six months and 12 months. In addition, the EBE group had a physical exam at three months if an endoleak was found at one month.

[Slide]

A variety of centers, 19 centers across the country including academic, non-academic and community hospitals and a variety of specialists for vascular disease were included in the study. Thank you.

Pivotal Study Clinical Results

DR. MATSUMURA: Good morning.

[Slide]

My name is Jon Matsumura. I am a paid consultant for W.L. Gore. I am also a

board-certified vascular surgeon and have concentrated most of my professional academic interest in endovascular therapy of aortic aneurysms. I am grateful for the privilege to work as the PI with the 19-site investigators in concert with the trial sponsor. It is also my pleasure to present the pivotal study data to you this morning.

[Slide]

Just to reiterate, the 12-month follow-up which I will be presenting you first had a data cut-off point in June of 2001. This included 260 patients in the EBE and 101 patients in the control group.

[Slide]

Let's go right to the pre-procedure results. These are clinical characteristics which were found to be significantly different between the two groups. Specifically, the EBE group had an average age that was three years older than the control group although there was a wide range. The EBE group had a higher proportion of men compared to the control group, and the EBE group had a lower proportion of patients with symptomatic abdominal aortic aneurysm.

There were many other clinical

characteristics that were evaluated to determine the comparability of the two treatment groups. This included a medical history of coronary-artery disease, arrhythmia, valvular heart disease, CHF, stroke, history of inflammatory aneurysm or family history of aneurysms or other aneurysms, history of peripheral arterial disease or prior vascular interventions, and none of these were different between the two groups.

[Slide]

Additional clinical characteristics that were compared include long-term steroid use, history of thrombotic event, emphysema, smoking history, renal failure or paralysis, erectile dysfunction in men, hepatic dysfunction, bleeding disorder and history of cancer. There were no differences between the two groups in any of these clinical characteristics.

[Slide]

We also used many of the Society-determined risk factor score systems such as the ASA by the anesthesiologists and the New York Heart Association, which had no differences between the two groups. The SVS joint societies risk factor score system is compared here. I will

point out that in the hyperlipidemia subcategory there was a difference and the EBE group had more hyperlipidemia than the control group, although there was no difference in the composite SVS risk score index between the two groups. Based on these comparisons, we figured that the two treatment groups are comparable.

[Slide]

We also looked at many anatomic variables as well as disease states for the arterial anatomy. Shown here are six that were significantly different between the two groups. The EBE group had an average aneurysm size 3 mm smaller than the control group. The proximal aortic neck was longer, narrower and had less angulation in the EBE group compared to the control group. The left and right common iliac arteries were smaller in the EBE group compared to the control group. These five differences would be expected given the protocol requirements for endovascular aneurysm repair.

I won't go through all of them but we studied 40 additional pretreatment anatomic and disease variables that are in the PMA and there are no differences between the treatment groups in these other variables.

[Slide]

This figure examines in more detail the differences in aneurysm size. Although there was a difference in mean aneurysm size between the EBE and the control group, you can see that a wide range of aneurysm sizes were treated in both groups. In addition, the majority of aneurysms were over 5 cm in size in both treatment groups.

[Slide]

Let's get to what the immediate procedure results are. In terms of EBE deployment evaluation at the initial procedure, there were 235 patients enrolled in the EBE group. All of the patients received one trunk ipsolateral leg and one contralateral leg and 100 percent deployment success. In addition to those components, a third or 32 percent of the patients had either one or more aortic extenders, one or more iliac extenders or one or more both aortic and iliac extenders as part of their initial treatment, all of which were deployed successfully.

[Slide]

Some of the immediate procedure results showed improved outcomes in the EBE and the control group and are shown here. The mean procedure time

was shorter in the EBE group. The mean blood loss was less compared to the controls, and the chance that you would require homologous blood transfusion was less in the EBE group compared to control.

[Slide]

We are going to go into the 12-month data, and before I show the results of the actual comparisons I want to show you the accountability. At one month these are the number of patients available who had not died, withdrawn or been lost to follow-up. At 12 months there are 81 controls and 215 EBE patients available for follow-up. You can see that we had over 90 percent compliance with follow-up clinical visits at the time points for each of the two treatment groups.

[Slide]

To remind you, our primary safety hypothesis was designed to evaluate major adverse events through the 12-month time point.

[Slide]

This is a breakdown, first, of the major adverse events in the two groups. If you look at any major adverse event, there were 57 percent of the control patients who had one and 14 percent of the EBE group, and this was a significant reduction

in major adverse events in the first 30 days.

When further breaking this down into organ systems or subgroups of major adverse events, this reduction of major adverse events was in several categories. In bleeding and pulmonary there was a 12-fold reduction. In cardiac there was a 4-fold reduction. In bowel, an 8-fold reduction and in vascular a 6-fold reduction in complications in the EBE group compared to the control group.

[Slide]

When you look at the major adverse events that occur between the 30-day time point and 12 months, 25 percent of the control group experienced one and 27 percent in the EBE group, which are not different rates. It is important to note that on the clinical events committee we considered interventions in the EBE group that were performed for endoleak or aneurysm enlargement where the patients stayed a day in the hospital, such as a coil embolization, as major adverse events in this group. If you look at the other categories broken down by organ system, there were no differences in the rate of adverse events after the 30-day time point to 12 months between EBE and the control group.

[Slide]

This figure puts those two data sets together and I am going to take some time to go through this. On the X axis is the months after procedure, 0, 12 or 14. On the Y axis is cumulative major adverse events as a rate per patient. The yellow curve is the EBE group; the white curve is the control group.

You can see that in the first 30 days there is a marked increase in the rate of adverse events in the control group compared to the EBE group. But after that time point these curves are relatively parallel and the ongoing rate of major adverse events after the first month is similar in the two groups.

Numerically, this can be seen here in this table. If you are in the control group you had an average of 1.2 major adverse events per patient in the first month. If you were in the EBE group you had an average of one event per five patients. At 12 months there continued to be a difference. You had a chance of 1.8 adverse events per patient in the control group and 0.9 adverse events in the EBE group. These are significantly different by a Nelson test.

[Slide]

Another way of comparing major adverse events is not just to look at how many complications you have on a per patient basis, but what is the chance that you will have any major adverse event. I think there might be concern that some patients have many adverse events so we also want to look at the proportion or the chance that you will have any or the first major adverse event.

This is a Kaplan-Meier depiction of that. Again, on the X axis is the time and on the Y axis freedom from first major adverse event. The yellow again is the EBE and the white is the control. At one month, again, there is a marked reduction in the chance of having even one major adverse event, from 86 percent in the EBE group to 43 percent in the control group. At 12 months the freedom from major adverse events continues to be different. There is a 62 percent chance in the EBE group of never having had a major adverse event and a 35 percent chance in the control group, and these are significant by log rank.

[Slide]

In addition to these univariable analyses, we conducted the multivariable analysis. This is

logistic regression looking at independent risk factors for early major adverse events and also to give you a risk-adjusted estimate of the risk associated with the treatment group.

Four risk factors were identified other than treatment group. A history of myocardial infarction, history of thrombotic event, and SVS pulmonary risk score of one or greater, and a lower platelet count were independent risk factors for early major adverse events. More importantly, we determined that the control group was a strong and independent risk factor for early major adverse events with a 12-fold odds ratio.

[Slide]

We did a similar multivariable analysis looking at late major adverse events. Using the Cox model, these five risk factors were found to be independent risk factors for late major adverse events: an older age, smaller body mass index, a history of prior vascular intervention, a history of symptomatic aneurysm and an increased proximal neck angle.

In this model we forced in-treatment group to see if it could predict late major adverse events and the EBE treatment group was not an

independent risk factor for late major adverse events.

[Slide]

We also looked at survival. Although the study wasn't powered to detect this it is of obvious interest. The survival is similar in the EBE and control groups. At 12 months the control group survival is 94 percent and 92 percent in the EBE group. These are not different.

[Slide]

We did a multivariable analysis to look at survival as well. These five risk factors were found to be independent risk factors for mortality in the Cox model. Again, an SVS pulmonary risk score of one or greater, a history of erectile dysfunction if you are a man, a lower platelet count, a lower initial ankle brachial index, and a larger difference between your maximum aneurysm diameter and proximal aortic diameter upon entry into the study. Again, we forced in-treatment group to see if there was any effect from treatment group allocation, and treatment group is not an independent risk factor for mortality.

[Slide]

Recently, reporting standards and the

evaluation of endovascular repair have been published out of the joint societies, and they defined a primary outcome measure of endovascular repair as aneurysm-related deaths. These would be defined as deaths due to aneurysm rupture, or related to the primary procedure, or a secondary procedure such as a later open surgical conversion.

We took a cautious interpretation of what "related" means and said that it is any death within 30 days of a primary or secondary procedure or during the same hospitalization. With this definition, we calculated aneurysm-related survival in the two groups. The survival curves are similar. There is a 98 percent aneurysm-related survival at one year in the control group and the EBE group.

[Slide]

In summary of our safety analysis, compared with open surgical repair for the primary treatment of aneurysm, the data demonstrate that EBE is safe. There is a lower rate of major adverse events, similar overall survival and similar aneurysm-related survival and there were no device-related deaths.

[Slide]

Just to remind you, we are going to switch to the efficacy evaluation. The hypothesis was based on evaluation exclusion from the blood circulation at 12 months, and it had those three components of endoleak, aneurysm size increase and device efficacy complications. I will go through each of them.

[Slide]

These are the endoleak rates from our core lab. The one month is in yellow; the 12 months is in grey. The majority of the patients did not have an endoleak. Of those who had an endoleak, most of the endoleaks were of the type II variety. There were some type I endoleaks at a lower frequency and some endoleaks at a lower frequency of indeterminate origin. There were no type III or type IV leaks found by the core lab.

[Slide]

Aneurysm diameter size change evaluation by the core lab is shown in this bar graph. Fourteen percent of the patients had an aneurysm size decrease of 5 mm or more; 79 percent of the patients had no change in their aneurysm size; 7 percent of the patients had an aneurysm size increase of 5 mm or more.

[Slide]

In addressing aneurysm size increase and endoleaks, it is important to note that during the course of this study the investigators met several times, at least annually in our investigator meetings, and we formed collectively a treatment guideline set, and this is it. We felt that aneurysms with type I endoleaks, type III endoleaks and enlargement regardless of endoleak status should be intensively studied and considered for catheter-based reintervention or conversion to open repair.

It is important that this consideration include the local investigator and the attending physician's assessment. As Dr. Brewster mentioned, there is still significant judgment used in the treatment of these patients and it includes the individual patient's co-morbidities, life expectancy and, of course, the patient's own personal choices. I would add that the endovascular treatment of aortic aneurysms is really an evolving process and these guidelines may change in the future.

[Slide]

These are the reinterventions that were

conducted during the first year in the pivotal study. There were 15 patients who had 17 reinterventions. Of the 15 patients, the majority of interventions were done for an endoleak but there was one patient who had a ligation performed, who had both an endoleak and aneurysm size increase, a ligation of a hypergastric artery. The other 16 procedures in the 14 patients were all catheter-based embolization procedures or other embolization procedures.

[Slide]

This is the third component of the efficacy hypothesis, the major device efficacy complications. I will go through this table slowly as well. There were no patients who had access failure. As mentioned, there was 100 percent deployment success. There were no intraoperative or early conversions in this group.

There were two patients who had occlusion of a branch artery, one early and one late. One was a hypergastric artery that was inadvertently occluded and led to lasting butt claudication. It was determined to be a major DEC. There was another patient who developed occlusion of the left renal artery and, at five weeks, underwent an

iliorenal bypass for that problem.

There were no patients found to have lumen obstruction or extrusion or erosion. No patients were found by the sites to have prosthetic material fatigue, and we will have more on that later. There was one patient who had prosthesis migration that required therapy with aortic cuffs. This patient had a main trunk component placed at the procedure. After deployment, it was noted later to move down a couple of centimeters caudally and an additional aortic extender was placed to treat that patient.

There were no patients with prosthesis realignment, and in the pivotal study there were no patients with aneurysm rupture. This, aneurysm rupture, is an important device efficacy complication, and I will point out that there is one rupture in the U.S. feasibility study; two ruptures in the European experience. The details are in your panel pack and perhaps we will explore those in the Q&A as well.

[Slide]

In summary of the device performance, there was 100 percent patency. There were no limb occlusions or clinical adverse events related to

device patency. There was 100 percent freedom from aneurysm rupture.

[Slide]

On this slide I am going to start from the bottom. If you take those three efficacy complications, you have 27 with endoleak at 12 months; 13 with aneurysm enlargement; and 3 that I just described with the major DECs, device efficacy complications. Because these 43 complications occurred in 38 patients, they are overlapping. That is how you get to 38 patients, and we used the denominator cautiously of 196 patients who had 12-month CT core lab data available, giving a primary efficacy success of 80.6 percent with these 95 percent confidence intervals. I will reiterate that these were based on core lab assessment for endoleak and aneurysm enlargement.

[Slide]

Our assessment of the efficacy data is that the EBE is an effective treatment method to exclude the aneurysm from the blood circulation.

[Slide]

The core lab looked at other imaging findings as well in its review of CTs and abdominal x-rays to evaluate device integrity, device patency

and trunk and component migration.

[Slide]

In terms of device integrity, the core lab identified a fracture in a discharge film of one patient, at a rate of 0.4 percent for that interval. No fractures were subsequently identified in the 12 months. I will discuss this fracture in the next slide. Again, because this is an important issue, device integrity or fractures, I will point out that there is one fracture in the second generation trial and there is a fracture identified in the European experience. Hopefully, we will discuss those in more detail during the Q&A.

[Slide]

In terms of the pivotal study, this patient had the fracture visible on the discharge film, which was the only x-ray performed in that patient. There were no clinical consequences. At 12 months a CT scan was performed and evaluated both by the site and the core lab, and no endoleak, no aneurysm enlargement, and no migration was identified. Unfortunately, the patient was diagnosed with inoperable liver cancer in the second year and died of this. No autopsy was

performed and the device is unavailable for analysis.

[Slide]

Some of the other core lab imaging findings--a small percentage of patients were identified by core lab review with device lumen narrowing; trunk migration of 10 mm or more relative to the arterial landmarks; and component migration of 10 mm or more relative to other components. In these patients there were no type I or type III endoleaks; no aneurysm enlargement; and no vascular adverse events or reinterventions.

[Slide]

We also had these secondary hypotheses which basically deal with how did the patients recover from the procedure.

[Slide]

These are the data on the secondary outcomes. The EBE patients had a 10-fold reduction in length of ICU stay; a 5-fold reduction in mean length of hospital stay; a reduction in time to ambulation; and also a reduction in the time to return to normal activities as reported by the patients themselves.

[Slide]

When you look at the pivotal study results and the 12-month endpoint compared to open surgery, the EBE is safe. We had 100 percent of the devices successfully deployed and patent. There was faster recovery; a striking reduction in major adverse events; similar survival both overall and aneurysm related. We had clinically effective aneurysm exclusion. There were no conversions in 12 months and no aneurysm ruptures.

[Slide]

In addition to the 12-month data showing the safety and effectiveness, we continued to follow these patients in the clinical trial, and I have the privilege also to present to you the 24-month data today to answer the question are the 12-month study results sustained.

[Slide]

This was rigorous and diligent follow-up at two years. Again, of the patients available for follow-up, we had over 90 percent compliance with the clinical visits in both treatment groups.

[Slide]

The survival curve going out to two years and 93 percent of the patients are still alive in that control group, 87 percent in the EBE. There

is no significant difference in these two.

[Slide]

Aneurysm-related survival, 98 percent in the control group, 98 percent in the EBE group at 24 months, no significant difference in aneurysm-related survival.

[Slide]

Endoleak results by the core lab are very similar. The majority of the patients do not have an endoleak. Of those who do have an endoleak--the 24-month data, by the way, is in grey; the 12-month in yellow. The majority of the endoleaks are the branch variety type. There is a small frequency of patients who have type I endoleak and endoleak of undetermined source. There were no type III or type IV endoleaks.

[Slide]

Aneurysm size change at 24 months--again, the 1-year data from 1-12 months is in gold or yellow; the grey is 1-24 months, and 19 percent of patients at 2 years have aneurysm size decrease of 5 mm or more. The majority of patients have no change in aneurysm size and 14 percent of the patients have aneurysm size increase of 5 mm or more.

[Slide]

There were 11 patients who had 12 reinterventions in the second year. Nine of those patients had catheter-based embolizations but I want to talk about the three who had late conversion to open repair. Two of these patients had aneurysm enlargement with no endoleak identified on preoperative imaging. One case had an endoleak and aneurysm enlargement, and this patient declined to have a catheter-based embolization. All three were converted to open surgical repair and were discharged. However, there is one unfortunate patient who was readmitted and actually died 24 days following the conversion of endocarditis. There were no signs of graft infection at the initial procedure with negative cultures. Many of the details on these patients are in your panel pack.

[Slide]

The other findings that the core lab is looking at are for integrity, lumen narrowing and migration, as shown here. In the 24-month follow-up no other wire-form fractures have been identified. A small percentage of patients have radiographic evidence of device lumen narrowing,

trunk migration or component migration but, again, there were no clinical consequences in any of these patients. There were no type I or type III endoleaks or aneurysm enlargement seen by the core lab, and no clinical vascular adverse events or reinterventions.

[Slide]

Again, this is our cumulative major adverse events rates now extended out to 24 months on the X axis. Again, the Y axis is the rate of adverse events per patient. You have seen the left half of this graph before. When you follow out the cumulative major adverse events, they continue to run essentially parallel. There is a persistent difference, 1.9 cumulative major adverse events per patient at two years in the control group compared to 1.1 adverse events per patient in the EBE group. Again, this is significantly different by the Nelson.

[Slide]

So, to answer the question about the 24-month data, what does it show? Are the 12-month results sustained? Yes, the 24-month data substantiates the findings of the 12-month data.

[Slide]

In conclusion, in this presentation of the pivotal study data, we feel that the EBE is safe and effective for treatment of abdominal aortic aneurysms and 100 percent of the devices were successfully deployed and patent. There was faster recovery. There is a striking and persistent reduction in major adverse events. There is similar survival both overall and aneurysm related. There is clinically effective aneurysm exclusion with rare conversions and no aneurysm ruptures. Thank you for your attention.

DR. LASKEY: I would like to thank and applaud this morning's presenters. You not only stayed on time but you are a tad early. Therefore, you have the privilege of responding to some early questioning from the panel.

[Laughter]

So, let's just take five minutes. Are there any burning questions from any of the panel members before we break for lunch?

DR. BAILEY: Could I just ask a quick one? I understand that the enrollment was parallel groups, all surgical candidates and then, according to their anatomy, they were divided into the two assigned treatments. I think I saw that the

statistical plan was to have a two to one ratio and, indeed, that seems to be close to what happened. Was this by chance or was there some mechanism to actually achieve this ratio? Or, is that just the natural ratio that comes in the door?

DR. MATSUMURA: I guess I will answer that question. The ratio is relatively two to one. The clinical criteria for enrollment were very similar. We didn't go through all those because they are in your pack and in the protocol and are similar to other trials. The only differences were where we showed the infrarenal anatomy had to meet the Excluder specifications, the EBE specifications in the test group, and in the control group they had to meet the criteria that an infrarenal clamp was planned.

I think that if you look across sites, there is a little bit of variation in the ratio of two to one. I don't know if it is in the panel pack but it is in the PMA, two to one. But sites were told ahead of time that that was our enrollment goal of two to one, and I suspect that as they were seeing patients, you know, that they had that in consideration.

I remember this meeting with the

investigators, and we had asked them not to be enrolling in other trials during their enrollment for this trial and to put all the patients who qualify in. So, I think it is rather fortuitous that that came out that way.

DR. BREWSTER: I think I would just add from a real-world clinical perspective in terms of the clinician interacting with the patient, once a site had enrolled an adequate number of control patients in the trial, I think the natural tendency of an investigator or center would be to not necessarily continue to enroll control patients because there is a certain follow-up burden, and so forth. So, once we felt at a particular site that an adequate number of controls had been enrolled, I think we probably ceased to enroll controls. That probably fosters the difference as well.

DR. LASKEY: Tony?

DR. COMEROTA: Jon, that was a very complete description of the results. My question is not burning but one of curiosity. You mentioned that proximal neck angle or increased proximal neck angle was an independent risk factor and I am presuming that that applies for the control group as well the EBE group. Now, the protocol design,

of course, excluded proximal neck angle of greater than 60 degrees in the EBE group. Is this new and interesting information that we can carry away that a neck angle increases risk for an operation in patients with abdominal aortic aneurysms?

DR. MATSUMURA: I think it is new information. I hope you don't carry it away because one of our investigators has plans to analyze that. But before this study was conducted and analyzed we couldn't find any significant anatomic predictors of risk in the literature, and we did a fairly extensive search, which is in the executive summary of the PMA and maybe in the panel pack. But many people have looked at clinical risk factors and, therefore, those are the ones that we really wanted to stratify. So, in our analysis, with Dr. Naftel's help, we did conduct this analysis really for risk adjustment and we wanted to include all the data that we had available, and we had extensive data on anatomy that was really very impressive in its detail and completeness. Of all the anatomic variables we tried to throw in the model, I think proximal neck angle only made it for late adverse events, not early and not survival.

But I think it is interesting. I can

remember that David called me up and said, well, why is this and what does a clinician think of this? I guess I am not going to write that paper; another sub-investigator is going to do that, but I suspect that it has something to do with more neck angulation being probably a marker for more advanced disease and perhaps either surgeons treat those patients because they have a larger aneurysm, or maybe it is just a marker that goes with something else about advanced disease. But I can't imagine that the neck angle itself makes it harder. The answer to your other question, is it applicable to control and EBE, I believe it is. It is for both groups.

DR. NAFTEL: I will just say that for all the models, in addition to analyzing all the patients together, in each case we applied the models to just the control and then just to the EBE to make sure there is no interaction and the results were consistent, and they were in each case.

DR. LASKEY: Ileana, one more question and then we will break for lunch.

DR. PINA: Just out of probably sheer ignorance, what do you do with anticoagulation? I

notice that some of the events that are labeled as stats for other issues came out of CBAs and peripheral embolization. How do you handle the anticoagulation?

DR. BREWSTER: There was a clinical adverse event committee that negotiated or considered adverse events, identified by Dr. Matsumura, the study primary investigator, which included all identifiable adverse events. The purpose was to better classify these, more accurately classify these in order to clarify reporting such as we have had this morning.

The initial study also had a rather large category of so-called "other" events. Another purpose of this adverse events committee, which met fairly often and included the primary investigator of the study itself, at least two site investigators and a member of the data safety monitoring board, reclassified these "other" events into appropriate categories, again, to better clarify reporting.

DR. PINA: Did you leave anticoagulation up to the investigators or did you have a set protocol? In other words, did the patients have to be on Coumadin for X number of days? Did they have

to be on aspirin? I mean, all these people have some sort of vascular disease.

DR. BREWSTER: There was no protocol requirement in terms of postoperative anticoagulation. That was left to whatever the standard practice of the investigator might be. I don't think any patients though were electively anticoagulated in terms of Coumadin, for instance. Many of them, no doubt, were put on aspirin. The protocol, in terms of perioperative management, was similar to standard open repair in that all patients were advised to undergo perioperative heparinization at the time of implant.

DR. LASKEY: Gentlemen, thank you. That was a very articulate presentation. Thank you for staying on time, and we will see you again at one o'clock. I would like to adjourn for lunch.

[Whereupon, at 12:00 noon the proceedings were recessed for lunch, to resume at 1:00 p.m.]

- - -

A F T E R N O O N P R O C E E D I N G S

DR. LASKEY: It is shortly after 1:00. We should resume. Let's reopen the session with the FDA presentation.

FDA Presentation

MR. GANTT: Good afternoon.

[Slide]

My name is Doyle Gantt. I am a senior biomedical engineer reviewer and one of the lead reviewers on this PMA application. Dorothy Abel is the other lead reviewer on this application.

[Slide]

My presentation will include the following, an introduction of the review team at FDA; a summary of the FDA review; and the questions for panel consideration. We had an opportunity to see the sponsor's presentation prior to their presentation this morning, and it accurately summarizes the data reviewed by the agency so these data will not be repeated in this presentation.

[Slide]

As with most PMAs like the one being discussed today, review of the documents involves a large number of reviewers that have provided reviews in their areas of expertise. Included were

clinical, statistical, in vivo, in vitro--

[Slide]

--as well as biocompatibility, packaging, sterilization, bioresearch monitoring, manufacturing, QSR regulation and patient labeling, and I would like to acknowledge all those individuals who contributed to the review of this application.

[Slide]

I would now like to begin with a summary of the FDA review of the application.

[Slide]

First let's start with the preclinical. FDA reviews of the biocompatibility, in vivo animal studies, manufacturing and sterilization information, including packaging and shelf-life, have been completed and there are no issues regarding these areas for the panel to discuss.

[Slide]

FDA review also included an assessment of the device integrity and there are a number of factors that I think we need to consider when looking at this issue. First of all, as with other stents used in the vascular system, endovascular grafts may be subject to conditions which may

result in loss of device integrity.

[Slide]

Another factor, depending upon the location and type of breach in integrity, there may or may not be an immediate or eventual clinical consequence. Another factor which must be considered in review of this issue is the difficulty in identifying and confirming the presence of structural failures in vivo. The sponsor didn't talk much about this in this morning's presentation, but in review of the failure analyses on this subject it became quite clear that these things are very difficult to view using standard x-ray techniques.

[Slide]

Prior to sending out the panel packs, there were two reports of wire-form fractures identified by the core laboratory, one at discharge in a patient enrolled in the Phase II study, and the other at 12 months in a patient enrolled in the ongoing second generation device study. As was mentioned by the sponsor this morning in their presentation, a second generation device study has been initiated to obtain data for a similar device. Although this device is not the subject of this

PMA, the device is comparable enough from a structural standpoint that we feel it is important to consider this as part of the review of this device as well.

[Slide]

Upon learning of these reports, the sponsor did conduct a failure analysis and they have communicated those findings to us. There have been no adverse effects associated with either of the two reports and there is not any conclusive evidence to verify the presence or absence of the fractures. As I mentioned earlier, they are very difficult to visualize using x-ray.

[Slide]

Both of these reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta, another factor that we believe is important in considering the significance of the integrity issue. The FDA review of the failure analysis of these two reports has been completed, with no additional information being requested of the sponsor.

[Slide]

Finally, the sponsor has recently reported

a fracture in an explanted device. The fracture was also located in the main body in the bifurcated region of the device and there is very limited information available at this time about this particular report.

[Slide]

Now I would like to switch gears a little bit and just go over a brief summary of the clinical review that was conducted by FDA. This is just an overview slide of the clinical study. As was mentioned earlier, the pivotal study provided primary safety and effectiveness data. As you heard in this morning's presentations, this was a non-randomized study with concurrent open surgical control, consisting of patients who were not eligible for treatment with endovascular graft due to anatomical restrictions.

[Slide]

Some of the notable issues that we addressed during the review of the clinical data included the appropriateness of the non-randomized study design; difficulty in enrolling patients, primarily because this is a male dominated disease; the number of, reasons for, and outcome of patients converted to open surgical repair; clarification of

the rate of major adverse events after one month; and clarification of the number of type I and III endoleaks and aneurysm enlargements.

[Slide]

In summary, all the FDA requests for additional information have been satisfied, and the review team has identified the following questions that we would like the panel to consider during their discussion of this application.

[Slide]

Question number 1, the primary safety endpoint of the clinical study was the rate of major complications as evaluated through 12 months. Additionally, data were presented for individual adverse effects, analyses were provided for risk factors associated with adverse events, and causes of death are provided. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of safety in the intended population.

[Slide]

Question number 2, the primary effectiveness endpoint of the clinical study was exclusion of the infrarenal abdominal aortic

aneurysm from the blood circulation defined by absence of aneurysm enlargement and endoleaks, as evaluated through 12 months. Additionally, data regarding potential problems associated with endovascular treatment, for example migration, aneurysm enlargement, endoleaks, ruptures, conversion, device integrity, are presented. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of effectiveness in the intended population.

[Slide]

Number 3, the core laboratory has reported two cases of wire-form fractures, one identified at discharge in a patient enrolled in the pivotal clinical study, and the other at 12 months in a patient enrolled in the ongoing second generation device study. There have been no adverse events associated with either report and there is not conclusive evidence to verify the presence or absence of the fractures. Both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta.

[Slide]

As a continuation, after the panel packs

were sent to the panel, the sponsor reported a wire-form fracture which was recently identified during the sponsor's analysis of a device explanted in Germany. Details concerning the length of implantation, implanting physician identity, and device lot and serial numbers remain unavailable. Based on the sponsor's analysis, it appears that the fracture, which was also located in the main body of the graft in the crotch of the bifurcation, did not result in any clinical complications and the ends of the wire did not appear to be protruding through the device material or the surrounding tissue. Please comment on the significance of these observations.

[Slide]

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events.

[Slide]

If the panel recommends approval for this device, then we would like the panel to address the

following questions concerning the label.

Does the indication for use, as stated below, adequately define the patient population studied, and for which the device will be marketed?

The Excluder Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease who have appropriate anatomy.

As a point of reference, we included an addendum to the panel questions that were sent out in the panel packs. That addendum includes the indications for use statement for each of the currently approved endovascular devices used in the treatment of AAA. For convenience, I have a series of slides that we can project during the panel discussion to make that discussion a little bit easier.

[Slide]

The second question related to the label, based on the clinical investigation experience, are there any additional warnings, precautions, or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts?

Again, I have a series of slides, which

was an addendum which was included in the panel pack, that describes the proposed label that the company has provided to us concerning the warnings, precautions and contraindications and we can project those if there is a need during the panel discussion to see the proposed label.

[Slide]

The third question related to the label, please comment on whether the instructions for use adequately describe how the device is to be delivered.

[Slide]

Finally, do you have any other comments on the label?

[Slide]

Question 5 is please comment on the adequacy of the proposed physician training plan, as described in the panel package.

[Slide]

Finally, the sponsor is proposing to conduct a post-approval study on the patients enrolled in the pivotal clinical study, that is, it started with 235 test patients and 99 controls. Five-year follow-up on all patients who are alive and not withdrawn from the study will be obtained

in accordance with the clinical protocol approved under the IDE for this device. Please comment on the acceptability of this plan, as briefly described in the panel package. As one final note on that matter, this is very consistent with the five-year post-approval studies being conducted by the other approved devices that are on the market.

With that, I will end my presentation and open it up for questions if there are questions of me, or if you would like to get started with the panel discussion that could happen as well.

DR. LASKEY: Does anybody have any questions for the presenter at this point? Dr. Pina?

DR. PINA: Thank you for your presentation. In your review you have a paragraph about the adjunctive procedures that were needed during the implementation. How does that compare to other similar devices on the market as far as percentage of adjunctive procedures that are needed at the time of implantation?

MR. GANTT: I am not sure of the response to that question. I might ask one of the other reviewers. Paul? Our clinical reviewer, Paul Chandeysson.

DR. CHANDEYSSON: My name is Paul Chandeysson. The rate of adjunctive procedures is relatively low for this type of device, seven percent.

DR. WHITE: Could I ask you another question before you leave? I was interested, and I am confused when I read the panel data, when you talked about the number of audited core laboratory images, specifically you talked about 155 paired CT images for aneurysm growth. Are you familiar with that part? Where did you get that information? I couldn't find that kind of audited information in the PMA. Where is the number of exams that were actually done to look at aneurysm growth? Is that somewhere in the PMA?

DR. CHANDEYSSON: I thought that was somewhere because that is where those numbers come from. It is possible it is an incorrect number but I thought that the number of paired CT studies was there.

DR. WHITE: The reason it is important is that the denominator becomes the frequency of the growth. So, your number of 155 paired studies is the only 155 I can find in the submission. Maybe the sponsor can help or the core laboratory can

help with that because that denominator number is going to end up being crucial in deciding what was the percentage of aneurysms that grew.

MR. GANTT: I might add something here. Keep in mind that you have an annotated version of the application. We have sent you a condensed version of the entire submission as the panel pack. I don't know if the sponsor wants to comment further.

DR. LASKEY: Well, not at this point; qe will get to that when we have them come to the table, but if there are questions for you specifically from the panel. Tony?

DR. COMEROTA: Will you address the statistical analysis either on safety or efficacy?

MR. GANTT: We didn't bring the statistician with us for that part of review, but if there are some general questions about the statistical review we would be happy to respond to that.

DR. WHITE: Well, most of us on the panel are not statisticians and the data as presented, from a clinician's perspective, looks reasonably compelling. Yet, there were some questions raised by the statistician, not regarding safety, of

course, but regarding efficacy and I just wanted to have that addressed if it were possible.

MR. GANTT: I believe the only thing that came up that was somewhat controversial in nature during the review, the statistical review, was one of the primary effectiveness endpoints and whether or not we would be able to allow a particular claim regarding the effectiveness of the device. Paul, do you have any further information about that and how we decided to resolve that?

DR. CHANDEYSSON: I think the issue was about whether the point value of the effectiveness, which was something above 80 percent, was sufficient or whether the lower 95 percent confidence interval would have to be considered, and that was below the projected 80 percent. That was the issue.

DR. LASKEY: If I am not mistaken, there was also a very important point made about surrogates that is worth emphasizing either now or later when we get to it. I must say just as a point of procedure, Dr. Zuckerman, we usually have a short little précis presented by the FDA statistician. We are just not having that today, and there are a few items of contention that it

would be worthwhile having--was it Gerry Gray? I forget who did this.

DR. ZUCKERMAN: You know, those points are noted, but Dr. Bailey is here to help us out.

DR. BAILEY: Yes, but I don't know anymore about what Dr. Kamer wrote. So, in his absence we will have to ask you guys.

DR. LASKEY: Well, that may fall out of the discussion. One more question, Ileana, and then we will move on to the primary reviewers.

DR. PINA: I am a little concerned about the deaths. I have been through each and every one of them that you listed in the packet here, and some of them that are listed as being pneumonia or sepsis are actually the result of a cardiac event and I counted several sudden deaths that were not classified as sudden deaths but if I looked at the history and I were sitting on an adjudication committee, they would be sudden death for whatever the etiology.

So, I am a little concerned about the cardiovascular risk here. I mean, these are patients who have extensive vascular disease and I am not entirely surprised, but I think they should be called what they are. Pneumonia is secondary to

the patient having been admitted with an arrest. There are also several CVAs, which is the reason I was asking about the anticoagulation protocol because if we are going to sit here and make recommendations and there are CVAs involved, and these patients have cruddy aortas and manipulation in there is going to, you know, let loose some stuff, I am very, very concerned about that.

There are obviously the cancers and all those that are way, way out, but some of these occurred within a month or two, the first event--unstable angina; there are some myocardial infarctions and I counted three or four sudden deaths. There are a couple of endocarditis. There is a pericarditis that actually sounds more like endocarditis than pericarditis. And these are things that we need to think about if we approve and when we are making the recommendations.

DR. ZUCKERMAN: I would like to make one correction. Although Mr. Gary Kamer isn't here to help us interpret the FDA's statistical review, Dr. Gerry Gray will be here this afternoon. Dr. Gray is our team leader for cardiovascular stats and he can answer questions that are brought up by the review done by Mr. Kamer.

DR. LASKEY: Thank you. Let's move on to have the panel present their discussion. The reviewers are Drs. Najarian and Comerota. Why don't we begin with Dr. Comerota? May we have the sponsor and their representatives step forward, please?

Open Committee Discussion

*DR. COMEROTA: Well, thank you very much. I will begin by congratulating the presenters for very elegant presentations and a review of the data, and also thank the reviewers for the FDA for a very complete summary, at least from my perspective.

In terms of the background of abdominal aortic aneurysms, I think perhaps Dr. Brewster's look at the risk of rupture was slightly pessimistic in terms of rupture, at least from the smaller sizes of the aneurysm. But I think what is also true is that despite attention to this entity the death rate from ruptured aneurysms over the last two to three decades has not diminished despite improvement in patient care when it is offered. Certainly, an operation is the standard by which all treatment modalities are to be judged.

We all recognize the advances in

technology and the zeal for endovascular repair of abdominal aortic aneurysms, as well as the pressure from the lay public to have this offered to them. So, certainly we can understand the reason for the design of the protocol being non-randomized, which certainly is a criticism of the protocol by any who might view it. Nonetheless, it certainly is understandable.

The device description and its delivery and the technique was well summarized, and the manufacturer recommends oversizing of somewhere between 10-21 percent of the graft to the aortic attachment, and somewhere between 5 and 26 percent for the iliac attachments.

The proposed indication was reviewed and the endoprosthesis, the EBE, was recommended for patients with appropriate anatomy. Just to redefine that, appropriate anatomy is an aortic neck of 1.5 cm or more, an angle of the aortic neck of 60 degrees or less and, of course, ilio-femoral morphology compatible with access and the delivery system and, of course, no thrombus at the aortic or the iliac implantation sites which might compromise the seal of the graft to the iliac artery interface.

The manufacturers presented their feasibility study which was performed in 30 patients, 28 men and two women. Then, following the feasibility study they proceeded to their controlled clinical trial. During follow-up of the feasibility study endoleaks were detected in 21 percent of the patients at three months; 25 percent at 6 months; and 20 percent of the patients at 12 months. An increase in size of the aneurysms in those patients in the feasibility study by 5 mm or more was observed in 17 percent by the 12-month follow-up, and that is by way of background of course.

One patient ruptured the aneurysm, a 77-year old woman who was essentially treated in violation of the study protocol in that her aortic neck angle measured 90 degrees at the time of implantation of the endograft. She had an endoleak identified. The recommendations were that she be converted to open repair. She refused any conversion to open repair and subsequently ruptured, I believe, three years later.

Another interesting patient is a 75-year old gentleman who demonstrated aneurysm growth at 36 months follow-up. The patient was converted to

open repair. There were elevated pressures measured in the aneurysm sac, however, no endoleak was identified at the time of open conversion. An interesting observation, in my opinion, was that there was serous fluid which was drained from the sac. The graft was intact. Gross and fluoroscopic examination of the explanted device did not reveal any perforation or fracture or device failure.

The last death was a 75-year old gentleman hospitalized with evidence of sepsis two months after the endograft was placed. Blood cultures were positive for Staph. aureus. The infected graft was removed successfully. The patient withdrew from the study during follow-up.

The control of the clinical trial was performed and the results were reviewed with us this morning in elegant fashion. The pivotal trial was a concurrently controlled clinical trial, not randomized. The patients met the inclusion and exclusion criteria, and those being suitable candidates for open repair of their aneurysm with intended placement of the aortic clamp in an infrarenal location.

I will address the underlying assumption that the complications of surgery were related to

the medical condition of the patient rather than the anatomy of the aortic aneurysm. It, therefore, appeared that a non-randomized control group such as this would offer reasonably valid comparison for the test group. I do challenge that underlying assumption that the anatomy of the aneurysm is not important in terms of an associated risk factor because, as it turned out, 11 percent of the control patients had suprarenal clamping of their abdominal aortic aneurysm during repair and I think most of us would agree that clamping of the aorta above the renal arteries would be associated with a high complication rate than infrarenal clamping in most centers.

There was a required sample size that was calculated upon the assumption that there would be a 10 percent complication rate in the test group and 25 percent complication rate in the control group. Then efficacy measures were calculated based upon the sample size.

That comes into play in terms of the efficacy analysis that was performed by the statistician and the conclusions from that statistical efficacy analysis, which I guess we should read into the record for completeness sake.

In terms of the risk of the surgical patients, I would just indicate that in my opinion I think the surgical patients in this trial were at increased risk compared to the non-operated patients, and that more patients were symptomatic in the surgical group. There were more females in the surgical group. The anatomic considerations were as I reviewed, with 11 percent of them having suprarenal clamping. This morning, in Dr. Matsumura's presentation, we learned that an increasing angle of the aortic neck was probably a long-term risk factor and, of course, by definition we had a greater angle in the surgical patients than the endograft patients. So, the assumption that anatomy is not an important risk consideration I believe is not particularly valid.

In the study, I think we have to compliment the investigators both endovascularly and surgically on achieving an exceptionally low operative mortality rate, one percent 30-day mortality rate in those patients undergoing endovascular repair and, as you saw, a zero percent 30-day mortality rate in the surgical group. But I don't think we, as surgeons, would agree that a zero percent mortality rate at 30 days means a zero

percent operative mortality. If we are critical of ourselves, we realize that there is a two percent operative mortality. Two patients died after the 30-day window but they did not survive the hospitalization for the aneurysm repair and died as a direct cause of complications that were experienced during their operation. That is an important consideration, of course.

In terms of the safety data, the principal safety analysis looks very favorable. The safety data were a comparison of the number of patient deaths, as well as other adverse events. I mentioned the 30-day mortality. The early adverse events commonly observed in the control group are calculated as 57 percent, and in the excluded group as 14 percent which, of course, was highly statistically significant. Interestingly and surprisingly to me, there were no open conversions reported before 24 months, another remarkable observation.

Three patients had conversions after the 24-month time period due to aneurysm enlargement, and no leak was found at the time of the open conversion in those patients. The observation of serous drainage or serous fluid within the aneurysm

sac in at least two of those three open conversions I thought was an interesting observation and raises a future question.

Follow-up CT scans regarding trunk migration, regarding component migration demonstrated an exceptionally low rate of true migration and component migration.

There were significantly fewer major adverse event rates in the Excluder group compared to the control group. The specific events that were individually significantly reduced are bleeding, pulmonary complications, cardiac complications and gastrointestinal complications, as were reviewed this morning.

The overall death rates I think we need to be cognizant of because during not only the one-year but during the entire follow-up period there was a 14 percent death rate in the endograft group compared to about a 17 percent death rate in the control group, and the overwhelming, if not all of those deaths, were not directly related to an aneurysm cause, aneurysm etiology or intervention for their aneurysm.

In terms of effectiveness of the Excluder Endoprosthesis in the management of aortic aneurysm

patients, there was 100 percent delivery rate. In 68 percent of the patients only the trunk ipsolateral and contralateral limb components of the device were required. The aortic extender was used in seven percent and one or more iliac extenders were used in 23 percent. Only three percent of the patients required both an aortic and iliac extender prosthesis.

We heard the results of the core laboratory reports regarding the presence of endoleaks. The number of endoleaks was relatively small, especially compared to other devices currently available. The number of type I endoleaks were preciously small by my observation.

In terms of secondary outcomes, it appears that secondary outcomes demonstrate significant benefit in the EBE group compared to the control group, this being reduction in blood loss; the reduction in the transfusion requirements; significantly more rapid procedure time and decreased length of ICU stay, reduced hospital stay; and quicker time to ambulation and recovery to patients' normal activities.

These observations are not in isolation. The European experience was reported. At the time

of the report that we received 234 patients were treated with the Excluder device and were entered into the EuroStar Registry from 33 centers. There were no conversions to surgery and there was no operative mortality in the patients entered into the EuroStar Registry. There was one potential aneurysm rupture several months following the deployment of the Excluder graft, and the reported rate of endoleak at 12 months in the EuroStar Registry was 11 percent.

So, from my perspective, it appears that, indeed, the EBE device met the requirements of safety. In terms of efficacy, from a clinician's perspective, it appears that it met the requirements for efficacy. However, as I reviewed the statistician's report, the FDA statistician's report, it did not meet the statistical requirements for efficacy based upon the a priori effectiveness goal set by the manufacturer of a rate of at least 80 percent. As I read the statistical analysis, that has to do with the confidence interval being somewhere between 77 percent and 95 percent rather than 80 and 95 percent. And, I am going to leave the statistical argument up to the rest of the panel, not must

myself, but I thought it important to read that into the record.

I would also make the point that while conversion to open surgery has been low, the majority of those patients who were converted with this particular device demonstrated an intact graft with no endoleak but with clear or serous fluid within the sac. I wonder if this is a unique property of the PTFE itself in terms of either allowing some serous drainage or promoting that type of response from the surrounding tissues, and perhaps this is something that we can address as a panel.

In terms of summary and my conclusions, I believe the sponsor of the Exclude Bifurcated Endoprosthesis has reported their data in a rather complete fashion including non-randomized controlled clinical trial of the Excluder versus conventional open surgical repair. It demonstrated significantly lower morbidity than conventional surgery for infrarenal abdominal aortic aneurysms. The mortality was very low in both groups and not different. The clinical utility endpoints such as blood loss, blood transfusions and those that I have summarized were significantly lower in the

Excluder Endoprosthesis group. So the device is safe and the rate of successful implantation is enviably high.

The effectiveness of the Excluder is measured by subsequent aneurysm rupture. That is very high. Only one patient suffered a ruptured aneurysm subsequent to attempted endograft placement but not in the controlled trial. That patient, as I mentioned, refused conversion. So, compared to other devices on the market the endograft treatment of abdominal aortic aneurysm with the Excluder appears to offer excellent safety and effectiveness with good durability.

I would also raise just one final question in terms of current data regarding the management of patients with aneurysms less than 5.5 cm. Of course, we are aware that two randomized trials have been published since the initiation of this trial, demonstrating that elective intervention of the "small" aneurysm demonstrated no benefit compared to careful surveillance. That may become an issue for subsequent management of all types of patients with aneurysms in the future, or may become an issue in terms of future trials looking at less invasive methods of management of patients

with smaller aneurysms compared to the natural history of those patients undergoing careful surveillance.

Mr. Chairman, that is my report. Thank you.

DR. LASKEY: Tony, do you have any specific questions you wanted to ask of the presenters today?

DR. COMEROTA: Well, one is the observation of that serous fluid within the sac in those who were converted that demonstrated no evidence of endoleak although the aneurysm was enlarging and there was increased pressure within the sac.

The other question, and I suspect that it may be a bit unfair to pose it, is in terms of are there going to be recommendations of management based upon size? And, will there be different considerations of intervention for an endoprosthesis compared to standard open repair for the patient with the smaller, i.e., less than 5.5 cm abdominal aortic aneurysm?

DR. MATSUMURA: Dr. Comerota, I think I will start with a response to the first question regarding the serous observation. I don't recall

the specific question but I think you are asking what do we think about that. You talked about four patients with conversion, and I just want to clarify that one of those was in the feasibility study and did not have an endoleak visible and had aneurysm enlargement, and the conversion was about three years later.

Three of the conversions that you spoke about were in the pivotal study. One of those patients did have a type II endoleak and refused a coil embolization. Presumably, that may be related to the growth. That patient, upon conversion, did well.

DR. COMEROTA: At the time of the conversion, however, the demonstration of the endoleak--correct me if I am in error, the demonstration of the endoleak was temporally removed from the conversion by quite a period of time, and at the time of conversion there was no demonstration of endoleak. Is that correct?

DR. BREWSTER: Could you say that again, Dr. Comerota?

DR. COMEROTA: If we are talking about the same patient, I believe that there was a patient who had an endoleak demonstrated early during the